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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,568	08/03/2001	Udo Baron	TTV-088CPADV2	9670

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,568	BARON ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-50,55 and 56* is/are pending in the application.

4a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,40-50,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 32-50, 55 and 56 are pending in the application. Claims 33-39 are withdrawn from consideration for being directed to non-elected subject matter. Claims 32, 40-50, 55 and 56 are currently under examination.

This Office Action is in response to the Amendment filed on 9/16/04.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/04 has been entered.

Response to Amendment

The objection warning of claims 52-54 for double patenting is moot in light of Applicant's cancellation of the claims.

The rejection of claim 51 under 35 U.S.C. 112 2nd paragraph is moot in light of Applicant's cancellation of the claim.

Claims 32, 40-50, 55 and 56 are rejected under 35 U.S.C.112 1st paragraph for reasons set forth of the record mailed on 1/16/04 and further discussed below.

Claims 32, 40-50, 55 and 56 are rejected under 35 U.S.C.101/112 1st paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 40-50, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this rejection, applicants argue that the pending claims do not require a phenotype, but rather recite that the transgene be expressed in cells of the transgenic animal at a level sufficient to produce amounts of the fusion protein that can activate transcription of the gene of interest at detectable levels. Applicants further argue that one of ordinary skill of art would be able to make and use the claimed non-human transgenic animal because the specification teaches in Example 3, graded transactivation of a luciferase reporter gene operably linked to the *tet* operator using the claimed fusion protein, wherein transcription of the luciferase gene depends upon activation by the TetR fusion protein. Applicants assert that the claimed gene expression system is a predictable system which provides a precise mechanism for controlling expression of a gene of interest in a detectable manner. Applicants further assert that the phenotype of the transgenic animal depends on the nature of the gene of interest and is the subject of scientists' hypothesis and is evaluated through the scientific process. Furthermore,

Applicants cited Bello et al., Bieschke et al., Melfi et al., and Ridgway et al. to demonstrate that the predictability of making transgenic animals comprising gene expression systems resulting in detectable expression of a gene of interest. Applicants assert that these references describes different transgenic animals, including Drosophila, Xenpus, flies and sea urchins, that comprises transcriptional regulatory system that is able to express gene of interest at detectable levels. Applicants argue that given that such transcriptional regulatory system functions in such phylogenetically diverse organisms, the claimed regulatory system of the claimed invention would also function in diverse organisms. Moreover, Applicants argue that the amount of experimentation is not undue because they are merely routine. Applicants further argue that one of skilled in the art would know how to use the claimed invention without a phenotype because a skilled artisan would recognize the advantage of the claimed invention for being a gene expression system with the ability to control transcription through graded transactivation, which is also described by Angeletti et al. and Shigehara et al. Applicants further cited Hasan et al. which describe transgenic mice wherein transactivator of the instant invention controls expression of the firefly luciferase gene in a study of noninvasive ways of imaging living mouse. Further, Applicants assert that Gallagher et al. describes kidney-specific expression of a transgene, and Pot et al. describes transgenic mouse with nogo A expression in Schwann cells. Applicants thus conclude that one of ordinary skill in the art would appreciate the advantages provided by the claimed invention in controlling gene expression in transgenic animals based on the teaching of the cited references. Therefore, Applicants assert that the claimed invention is enabled to its full scope.

These arguments have been fully considered but deemed unpersuasive. The claimed invention is not enabled by the instant specification for reasons set forth of the record mailed on 7/15/03 and 1/16/04. As discussed in the previous office actions, the rejection is based on how to make and use the invention in commensurate with the scope of the claim. The phenotype of the claimed transgenic animal is essential to the enablement of the claimed invention because one skilled in the art would not know how to use a transgenic animal with claimed genotype, but shows no phenotypic feature. The Examiner would like to clarify that the word phenotype does not necessarily mean a specific diseased symptom, but rather the feature the transgenic animal displays as the result of the integration of the transgene such that distinguishes it from a normal animal. As discussed in the previous office action, Mullin et al. teaches that the major problem regarding pronuclear injection (as suggested by the specification) is that the exogenous DNA integrates randomly into chromosomal DNA. Positional effects, where the transgene is influenced by its site of integration in the host chromosome can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene. Such problem would affect the level of expression of the fusion protein in the transgenic animal, thus it is unpredictable whether the claimed transgenic animal would produce the fusion protein at high enough level that can regulate the transcription of another gene and produces a phenotype. The teaching of the specification in Example 3 does not overcome such unpredictability because it is directed to *in vitro* cell culture rather than in a transgenic animal system. The examiner would maintain that based on the teaching of the prior art, the phenotype of a transgenic animal is unpredictable.

Further, one skilled in the art would not know how to use the transgenic animal without any phenotype.

Bello et al., Bieschke et al., Melfi et al., and Ridgway et al. are cited by Applicants to demonstrate the predictability of making transgenic animals comprising gene expression systems resulting in detectable expression of a gene of interest. These references have been fully considered, however, they are not sufficient to overcome this rejection for following reasons. First, although the so called transcriptional regulatory system are functional in Drosophila, sea urchin and xenopus, Applicants are reminded that such transgenic system is rather different to other higher transgenic non-human system such as mammalian system as claimed (for example, mouse, cow, sheep). The unpredictability of make and use transgenic mammalian system as claimed is discussed above. The demonstration of a transgene activation in Drosophila, sea urchin and xenopus is not sufficient to enable the claimed invention to its full scope since the claimed encompasses all transgenic non-human animal. Second, the cited references only demonstrate the activation of an exogenous reporter gene. None of the references provides support for the enablement of regulating expression of an endogenous gene. As such, the cited references do not overcome the art-recognized unpredictability as discussed above.

In response to Applicants' argument regarding routine experimentation, The examiner would like to point out that although the making a transgenic animal following the teaching of the specification is routine at the time of filing, generating any transgenic animal including not only lower eukaryotic organisms but also higher animal such as mammal with the predicted outcome of regulating any gene expression in commensurate

with the scope of the claim is not routine experimentation based on the art recognized unpredictability. As such, one skilled art would have to engage in undue experimentation to make and use the invention in commensurate with the scope of the claim.

The teaching of Angeletti et al., Shigehara et al., Hasan et al., Gallagher et al. and Pot et al. is fully considered. However, contrary to Applicant's assertion, these references also fail to enable the instantly claimed invention. The transcriptional regulatory systems taught by Angeletti et al., Shigehara et al., Hasan et al. are limited to regulating an exogenous reporter gene in transgenic mouse. The demonstration of such regulatory system in one species with regard to only exogenous reporter gene does not extend the predictability to all gene of interest in all transgenic animals for reasons discussed above. In fact, Hasan et al. also state that "in spite of exciting perspectives opened up by systems that permit conditional activity of transgenes, concerns remain regarding status of transgene expression, which may vary even among individuals of highly inbred mouse lines possibly due to epigenetic effects." (See page 116, 1st col., 1st paragraph, lines 13-18). Pot et al. describes transgenic mouse with *nogo* A expression in Schwann cells which is rather different from the claimed invention in which a fusion protein is expressed and in turn regulates the expression of a gene of interest. Lastly, although Gallagher et al. demonstrate kidney-specific expression of a transgene regulated by a rather different system as the claimed invention, again, such success is limited to a reporter gene. Gallagher et al. further tested expression of a human PKD2 cDNA in the transgenic mouse, however, the expression of the gene fails to produce any phenotype as predicted, producing cyst after 6 month (see abstract and page 2051, 1st col., last paragraph). Gallagher et al. assert four possible explanation for this result, including the

transgene has not reach high enough level. Therefore, in year 2003, 6 years after the priority date of the instant application, the successful generation of a transgenic mouse with a specific phenotype is still unpredictable. As such, without teaching from the specification and guidance from the prior art, one skilled in the art would have to engage in undue experimentation to make and use the claimed invention. The rejection is thus maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

Claims 32, 40-50, 55 and 56 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a transgenic animal comprising a transgene encoding a fusion protein which activates transcription of a gene of interest operatively linked to a target DNA sequence to which the fusion protein binds, wherein the fusion protein comprises a first polypeptide comprising a transcriptional activation domain and a second polypeptide comprises at least one copy of a HSV VP16 from position 436-447 and having mutation of position 442, wherein the transgene being expressed in cells of the transgenic animal at a sufficient level to produce amounts of fusion protein that can activate transcription of the gene of interest at detectable level.

A search of the prior art does not yield such a system with well established utility. The specification teaches that the claimed transgenic animal is useful for studying transcriptional regulation. However, the utility guideline requires the claimed invention

to have a specific substantial utility. The utility for studying transcriptional regulation is not specific to the instant invention because many other regulatory systems can serve this purpose. The specification also fails to teach any specific gene of interest which is regulated by this system so that the claimed invention would have a substantial utility. As demonstrated in the cited prior art, the gene of interest is limited to reporter genes, the utility of such system is not substantial. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, this asserted utility is not specific and substantial. Therefore, it is not considered as a patentable utility.

Claims 32, 40-50, 55 and 56 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian
Examiner
Art Unit 1636